

Applicants have amended the specification at page 1 to cross-reference the present application to related earlier applications.

Applicants have amended the claims in response to the Examiner's restriction requirement and objections and to improve their form.

Specifically, applicants have amended claim 1 to overcome the Examiner's objections (see below). Additionally, to correct recursive definitions in claim 1, applicants have amended the definition of radical R⁸ to recite "Ht'" rather than "Ht" as one of the embodiments. Support for added radical Ht' is found in the definition of Ht. Added radical Ht' recites "Q'" rather than "Q". Support for added radical Q' is found in the definitions of Ht and Q. Applicants have also amended the definition of radical Y' in claim 1 to recite "Y'", rather than "Y" at page 369, line 24. The recitation of "Y" was clearly an inadvertent typographical error. One of ordinary skill in the art would readily realize that the recitation of "Y" should have been "Y'", since Y is defined as "P or S" and therefore has no carbon atoms. Applicants have also amended the definition of E in claim 1 to delete superfluous recitation of "-O-Ht" (included in "-O-R³") and "-N(R²)-Ht" (included in "-N(R²)(R³)").

Applicants have amended claims 2-3 to incorporate the amendments to claim 1. Support for these amendments is found in original claims 2-3, respectively.

Applicants have canceled claim 6, which was directed to non-elected subject matter.

Applicants have amended claims 4 and 11 to refer to embodiments in the alternative. Applicants have amended claims 8-9 to improve their form.

Applicants have amended claims 15-16 to delete compounds that fall outside the scope of amended claim 1, namely, compound numbers 18-20, 22, 24-25, 58 and 68-69. Applicants have also amended claims 15-17 to recite chemical structures of compounds therein, in addition to their compound numbers. Support for these amendments is found in Tables 1-3 at pages 31-55 of the specification.

Applicants have amended claim 18 to delete its dependency from canceled claim 6.

Applicants have amended claim 21 to overcome the Examiner's 35 U.S.C. § 112, second paragraph rejection. Applicants have also amended claim 21 to delete the second occurrence of "phosphonoformic acid".

Applicants have added claim 28 to recite subject matter canceled from amended claim 21. Support for added claim 28 is found in original claim 21 and at page 73, line

28 to page 75, line 3 of the specification as originally filed.

Applicants have amended claim 22 to depend from added claim 28, in addition to claims 18-21. Support for this amendment is found in original claims 21-22.

None of the above amendments adds any new subject matter.

THE RESTRICTION REQUIREMENT

The Examiner has required restriction of the claims in this application under 35 U.S.C. § 121 to one of the following groups:

Group I: Claims 1-22, drawn to compounds of formula I; and

Group II: Claims 23-27, drawn to methods of using compounds of formula I.

In a May 9, 2001 telephone conversation with the Examiner, applicants' representative, Ms. Lisa A. Dixon, provisionally elected Group I, claims 1-22 for further prosecution and elected compound 59 with traverse. Applicants affirm this provisional election.

Applicants may request rejoinder of claims 23-27 with the elected group if and when any of claims 1-22 are

found allowable. MPEP § 821.04. Accordingly, applicants have not canceled these claims.

THE OBJECTIONS TO CLAIMS 1-22

The Examiner has objected to claims 1-22 as containing non-elected subject matter. Specifically, the Examiner has stated that claims 1-22 are generic to a plurality of disclosed patentably distinct species. Pursuant 35 U.S.C. § 121, the Examiner has set forth the following generic concept based on applicants' elected species (compound 59) for further prosecution: A is tetrahydrofurodihydrofuranyl-O-C(O)-; D is -C₁-C₆ alkyl-C₃-C₆ cycloalkyl wherein the cycloalkyl portion is optionally substituted, or -C₁-C₆ alkyl which is substituted with a 3-7 membered saturated, partially saturated or unsaturated carbocyclic ring system;[†] x in (G)_x is 1; G is selected from H, R⁷ or C₁-C₄ alkyl; D', E, n, R¹-R⁹, R³³, Q, M, M', W, X, Y and Z are as defined; and n, R¹-R⁹, Q, M, M', W, X, Y, Y' and Z are commensurate in scope with the elected embodiment for A, D and G. The Examiner has suggested that applicants

[†] During a telephonic conversation with the Examiner on August 15, 2001 regarding the clarification of the definition of D, the Examiner informed applicants of the change in the D definition, as summarized herein.

direct the claims to the subject matter of this generic concept.

To expedite prosecution, applicants have amended claim 1 to recite subject matter directed to the Examiner's generic concept. Specifically, applicants have amended radical A to recite "tetrahydrofuro-dihydrofuranyl-O-C(O)-" only; radical D to recite "C₁-C₆ alkyl substituted with Q," wherein Q is independently selected from a 3-7 membered saturated, partially saturated or unsaturated carbocyclic ring system; radical G to recite "H, R⁷ or C₁-C₄ alkyl" and radical x to recite "x in (G)_x is 1". Consistent with these amendments, applicants have amended claim 1 to cancel the recitation of radical R¹, because it is redundant upon elimination of the non-elected subject matter.

Thus, claim 1 as amended and claims that depend therefrom contain only elected subject matter. The cancellation of non-elected subject matter is expressly without waiver of applicants' rights to file divisional or continuing applications directed to the canceled subject matter and claiming priority herefrom under 35 U.S.C. § 120.

In view of the above amendments, applicants respectfully request that the Examiner withdraw the objections to claims 1-22.

THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH:

The Examiner has rejected claims 4 and 21 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Applicants address each of the issues raised by the Examiner below.

Claim 4

The Examiner asserts that claim 4 is indefinite because the structures in claim 4 are not referred to in the alternative. Applicants have amended claim 4 to insert the word "or" between the last two depicted structures and to insert a period after the last structure, as suggested by the Examiner.

Claim 21

The Examiner asserts that claim 21 is indefinite because the phrase "such as" renders the claim unclear as to whether the limitations following the phrase are part of the claimed invention. Applicants have deleted each occurrence of the phrase "such as," as well as the phrases immediately following each occurrence. In addition, applicants have added claim 28 directed to the subject matter canceled from claim 21.

In view of the above, applicants respectfully request that the Examiner withdraw these § 112, second paragraph rejections.

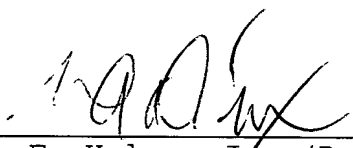
CONCLUSION

In view of the foregoing remarks and amendments, applicants request that the Examiner favorably reconsider this application and allow the claims pending herein. If the Examiner believes that a telephone conference would expedite allowance of this application, she is invited to telephone applicants' attorneys at (212) 596-9000.

Respectfully submitted,

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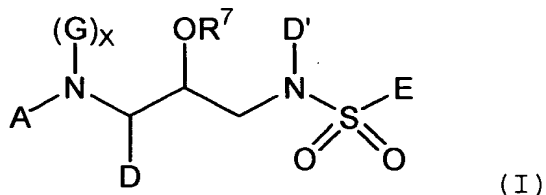
August 22, 2001
Lucinda Corb
Lucinda J. Corb
Signature of Person Signing


James F. Haley, Jr. (Reg. No. 27,794)
Lisa A. Dixon (Reg. No. 40,995)
Attorneys for Applicants
c/o FISH & NEAVE
Customer No. 1473
1251 Avenue of the Americas
50th Floor
New York, New York 10020-1104
Tel: (212) 596-9000

APPENDIX OF AMENDMENTS

IN THE CLAIMS

1. (Amended) A compound of the formula (I):



and pharmaceutically acceptable salts thereof; wherein:

A is [selected from H; Ht; -R¹-Ht; -R¹-C₁-C₆ alkyl, which is optionally substituted with one or more groups independently selected from hydroxy, -CN, C₁-C₄ alkoxy, Ht, -O-Ht, -NR²-Ht, -NR²-CO-N(R²)₂, -SO₂-N(R²)₂, -SO₂-R² or -CO-N(R²)₂; -R¹-C₂-C₆ alkenyl, which is optionally substituted with one or more groups independently selected from hydroxy, C₁-C₄ alkoxy, Ht, -O-Ht, -NR²-CO-N(R²)₂ or -CO-N(R²)₂; or R⁷]; tetrahydrofurodihydrofuranyl-O-C(O)-, wherein tetrahydrofurodihydrofuranyl is optionally substituted with one or more substituents independently selected from oxo, -OR², SR², -R², -N(R²)(R²), -R²-OH, -CN, -CO₂R², -C(O)-N(R²)₂, -S(O)₂-N(R²)₂, -N(R²)-C(O)-R², -N(R²)-C(O)O-R², -C(O)-R², -S(O)_n-R², -OCF₃, -S(O)_n-Q, methylenedioxy, -N(R²)-S(O)₂(R²), halo, -CF₃, -NO₂, Q, -OQ, -OR⁷, -SR⁷, -R⁷, -N(R²)(R⁷) or -N(R⁷)₂;

[each R¹ is independently selected from -C(O)-, -S(O)₂-, -C(O)-C(O)-, -O-C(O)-, -O-S(O)₂-, -NR²-, -NR²-S(O)₂-, -NR²-C(O)- or -NR²-C(O)-C(O)-];

each Ht is independently selected from C₃-C₇ cycloalkyl; C₅-C₇ cycloalkenyl; C₆-C₁₄ aryl; or a 5-7 membered saturated or unsaturated heterocycle, containing one or more heteroatoms selected from N, N(R²), O, S and S(O)_n; wherein said aryl or said heterocycle is optionally fused to Q; and wherein any member of said Ht is optionally substituted with one or more substituents independently selected from oxo, -OR², SR², -R², -N(R²)(R²), -R²-OH, -CN,

$-\text{CO}_2\text{R}^2$, $-\text{C}(\text{O})-\text{N}(\text{R}^2)_2$, $-\text{S}(\text{O})_2-\text{N}(\text{R}^2)_2$, $-\text{N}(\text{R}^2)-\text{C}(\text{O})-\text{R}^2$, $-\text{N}(\text{R}^2)-\text{C}(\text{O})\text{O}-\text{R}^2$, $-\text{C}(\text{O})-\text{R}^2$, $-\text{S}(\text{O})_n-\text{R}^2$, $-\text{OCF}_3$, $-\text{S}(\text{O})_n-\text{Q}$, methylenedioxy, $-\text{N}(\text{R}^2)-\text{S}(\text{O})_2(\text{R}^2)$, halo, $-\text{CF}_3$, $-\text{NO}_2$, Q , $-\text{OQ}$, $-\text{OR}^7$, $-\text{SR}^7$, $-\text{R}^7$, $-\text{N}(\text{R}^2)(\text{R}^7)$ or $-\text{N}(\text{R}^7)_2$;

each R^2 is independently selected from H, or $\text{C}_1\text{-C}_4$ alkyl optionally substituted with a 3-7 membered saturated, partially saturated or unsaturated carbocyclic ring system; or a 5-7 membered saturated, partially saturated or unsaturated heterocyclic ring containing one or more heteroatoms selected from O, N, S, $\text{S}(\text{O})_n$ or $\text{N}(\text{R}^{33})$; wherein any of said ring systems or $\text{N}(\text{R}^{33})$ is optionally substituted with 1 to 4 substituents independently selected from $-\text{X}'-\text{Y}'$, $-\text{O-arylalkyl}$, $-\text{S-arylalkyl}$, $-\text{N}(\text{Y}')_2$, $-\text{N}(\text{H})\text{-arylalkyl}$, $-\text{N}(\text{C}_1\text{-C}_4\text{ alkyl})\text{-arylalkyl}$, oxo, $-\text{O-}(\text{C}_1\text{-C}_4\text{ alkyl})$, OH, $\text{C}_1\text{-C}_4$ alkyl, $-\text{SO}_2\text{H}$, $-\text{SO}_2\text{-(C}_1\text{-C}_4\text{ alkyl)}$, $-\text{SO}_2\text{-NH}_2$, $-\text{SO}_2\text{-NH}(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{SO}_2\text{-N}(\text{C}_1\text{-C}_4\text{ alkyl})_2$, $-\text{NH}_2$, $-\text{NH}(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{N}(\text{C}_1\text{-C}_4\text{ alkyl})_2$, $-\text{NH-C}(\text{O})\text{H}$, $-\text{N}(\text{C}_1\text{-C}_4\text{ alkyl})\text{-C}(\text{O})\text{H}$, $-\text{NH-C}(\text{O})\text{-C}_1\text{-C}_4\text{ alkyl}$, $-\text{C}_1\text{-C}_4\text{ alkyl-OH}$, $-\text{OH}$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{O-C}_1\text{-C}_4\text{ alkyl}$, $-\text{C}(\text{O})\text{-NH}_2$, $-\text{C}(\text{O})\text{-NH}(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{C}(\text{O})\text{-N}(\text{C}_1\text{-C}_4\text{ alkyl})_2$, halo or $-\text{CF}_3$;

X' is $-\text{O-}$, $-\text{S-}$, $-\text{NH-}$, $-\text{NHC}(\text{O})\text{-}$, $-\text{NHC}(\text{O})\text{O-}$, $-\text{NH}\text{SO}_2\text{-}$, or $-\text{N-}(\text{C}_1\text{-C}_4)\text{alkyl-}$;

Y' is $\text{C}_1\text{-C}_{15}$ alkyl, $\text{C}_2\text{-C}_{15}$ alkenyl or alkynyl, wherein one to five carbon atoms in $[\text{Y}] \text{Y}'$ are optionally substituted with $\text{C}_3\text{-C}_7$ cycloalkyl or $\text{C}_5\text{-C}_6$ cycloalkenyl, $\text{C}_6\text{-C}_{14}$ aryl or a 5-7 membered saturated or unsaturated heterocycle, containing one or more heteroatoms selected from N, NH, O, S and $\text{S}(\text{O})_n$;

each R^3 is independently selected from H, Ht, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_6$ cycloalkyl or $\text{C}_5\text{-C}_6$ cycloalkenyl; wherein any member of said R^3 , except H, is optionally substituted with one or more substituents selected from $-\text{OR}^2$, $-\text{C}(\text{O})-\text{N}(\text{R}^2)_2$, $-\text{S}(\text{O})_n-\text{N}(\text{R}^2)_2$, $-\text{N}(\text{R}^2)_2$, $-\text{N}(\text{R}^2)-\text{C}(\text{O})\text{O}(\text{R}^2)$, $-\text{N}(\text{R}^2)-\text{C}(\text{O})\text{N}(\text{R}^2)_2$, $-\text{N}(\text{R}^2)-\text{C}(\text{O})-\text{R}^2$, Ht, $-\text{CN}$, $-\text{SR}^2$, $-\text{C}(\text{O})\text{OR}^2$, or $\text{N}(\text{R}^2)-\text{C}(\text{O})-\text{R}^2$;

each R^{33} is selected from H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl or C_5 - C_6 cycloalkenyl, C_6 - C_{14} aryl or a 5-7 membered saturated or unsaturated heterocycle, containing one or more heteroatoms selected from N, NH, O, S and $S(O)_n$;

each n is independently 1 or 2;

G[, when present,] is selected from H, R^7 or C_1 - C_4 alkyl[, or, when G is C_1 - C_4 alkyl, G and R^7 are bound to one another either directly or through a C_1 - C_3 linker to form a heterocyclic ring; or

when G is not present (i.e., when x in $(G)_x$ is 0), then the nitrogen to which G is attached is bound directly to the R^7 group in $-OR^7$ with the concomitant displacement of one -ZM group from R^7];

x in $(G)_x$ is 1;

D is [selected from] C_1 - C_6 alkyl [which is] substituted with Q, [which] wherein said alkyl is optionally substituted with one or more groups selected from C_3 - C_6 cycloalkyl, $-R^3$, $-O-Q$ or Q; [C_2 - C_4 alkenyl which is substituted with Q, which is optionally substituted with one or more groups selected from $-OR^2$, $-S-Ht$, $-R^3$, $-O-Q$ or Q; C_3 - C_6 cycloalkyl, which is optionally substituted with or fused to Q; or C_5 - C_6 cycloalkenyl, which is optionally substituted with or fused to Q;]

each Q is independently selected from a 3-7 membered saturated, partially saturated or unsaturated carbocyclic ring system; [or a 5-7 membered saturated, partially saturated or unsaturated heterocyclic ring containing one or more heteroatoms selected from O, N, S, $S(O)_n$ or $N(R^2)$];] wherein Q contains one substituent selected from $-OR^2$, $-OR^8$, $-O$ -arylalkyl, $-SR^8$, $-S$ -arylalkyl, $-N(R^2)R^8$, $-N(R^2)$ -arylalkyl and may be optionally substituted with one or more additional substituents independently selected from oxo, $-OR^8$, $-O$ -arylalkyl, $-SR^8$, $-S$ -arylalkyl, $-N(R^2)R^8$, $-N(R^2)$ -arylalkyl, $-OR^2$, $-R^2$, $-SO_2R^2$, $-SO_2-N(R^2)_2$, $-N(R^2)_2$,

$-N(R^2)-C(O)-R^2$, $-OH$, $(C_1-C_4)-OH$, $-CN$, $-CO_2R^2$, $-C(O)-N(R^2)_2$, halo or $-CF_3$;

each R^8 is independently selected from $[Ht,] \underline{Ht'}$, $-C_1-C_{15}$ branched or straight chain alkyl, alkenyl or alkynyl wherein one to five carbon atoms in said alkyl, alkenyl or alkynyl are independently replaced by W, or wherein one to five carbon atoms in said alkyl, alkenyl or alkynyl are substituted with $[Ht] \underline{Ht'}$; and wherein R^8 is additionally and optionally substituted with one or more groups independently selected from $-OH[,]_i$, $-S(C_1-C_6 \text{ alkyl})[,]_i$, $-CN[,]_i$, $-CF_3[,]_i$, $-N(R^2)_2[,]_i$, halo[,]_i, $-C_1-C_4\text{-alkyl}[,]_i$, $-C_1-C_4\text{-alkoxy}$; $[-Ht; -O-Ht;] \underline{-Ht'; -O-Ht'}$; $-NR^2-CO-N(R^2)_2$; $-CO-N(R^2)_2$; $-R^1-C_2-C_6$ alkenyl, which is optionally substituted with one or more groups independently selected from hydroxy, C_1-C_4 alkoxy, $[Ht, -O-Ht,] \underline{-Ht', -O-Ht'}$, $-NR^2-CO-N(R^2)_2$ or $-CO-N(R^2)_2$; or R^7 ;

wherein W is $-O-$, $-NR^2-$, $-S-$, $-C(O)-$, $-C(S)-$, $-C(=NR^2)-$, $-S(O)_2-$, $-NR^2-S(O)_2-$, $-S(O)_2-NR^2-$, $-NR^2-C(O)O-$, $-O-C(O)NR^2-$, $-NR^2-C(O)NR^2-$, $-NR^2-C(S)NR^2-$, $-CONR^2$, $-NR^2C(O)-$, $-C(S)NR^2$, $-NR^2C(S)-$, $-NR^2-C(=N-CN)-NR^2-$, $-NR^2C(=N-CN)O-$ or $-C(O)O-$;

each Ht' is independently selected from C_3-C_7 cycloalkyl; C_5-C_7 cycloalkenyl; C_6-C_{14} aryl; 5-7 membered saturated or unsaturated heterocycle containing one or more heteroatoms selected from N, $N(R^2)$, O, S and $S(O)_n$; wherein said aryl or said heterocycle is optionally fused to Q' ; and wherein any member of said Ht' is optionally substituted with one or more substituents independently selected from oxo, $-OR^2$, SR^2 , $-R^2$, $-N(R^2)(R^2)$, $-R^2-OH$, $-CN$, $-CO_2R^2$, $-C(O)-N(R^2)_2$, $-S(O)_2-N(R^2)_2$, $-N(R^2)-C(O)-R^2$, $-N(R^2)-C(O)O-R^2$, $-C(O)-R^2$, $-S(O)_n-R^2$, $-OCF_3$, $-S(O)_n-Q'$, methylenedioxy, $-N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$, $-NO_2$, Q' , $-OQ'$, $-OR^7$, $-SR^7$, $-R^7$, $-N(R^2)(R^7)$ or $-N(R^7)_2$;

each Q' is independently selected from a 3-7 membered saturated, partially saturated or unsaturated

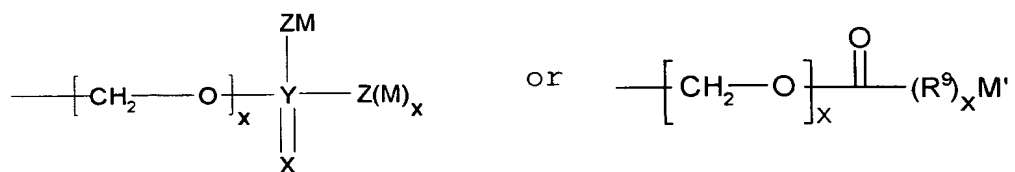
carbocyclic ring system; or a 5-7 membered saturated, partially saturated or unsaturated heterocyclic ring containing one or more heteroatoms selected from O, N, S, S(O)_n or N(R²);

D' is selected from C₁-C₁₅ alkyl, C₁-C₁₅ alkoxy, C₂-C₁₅ alkenyl, C₂-C₁₅ alkenyloxy, C₂-C₁₅ alkynyl, or C₂-C₁₅ alkynyloxy, wherein D' optionally comprises one or more substituents independently selected from Ht, oxo, halo, -CF₃, -OCF₃, -NO₂, azido, -SH, -SR³, -N(R³)-N(R³)₂, -O-N(R³)₂, -(R³)N-O-(R³), -N(R³)₂, -CN, -CO₂R³, -C(O)-N(R³)₂, -S(O)_n-N(R³)₂, -N(R³)-C(O)-R³, -N(R³)-C(O)-N(R³)₂, -C(O)-R³, -S(O)_n-R³, -N(R³)-S(O)_n(R³), -N(R³)-S(O)_n-N(R³)₂, -S-NR³-C(O)R³, -C(S)N(R³)₂, -C(S)R³, -NR³-C(O)OR³, -O-C(O)OR³, -O-C(O)N(R³)₂, -NR³-C(S)R³, =N-OH, =N-OR³, =N-N(R³)₂, =NR³, =NNR³-C(O)N(R³)₂, =NNR³-C(O)OR³, =NNR³-S(O)_n-N(R³)₂, -NR³-C(S)OR³, -NR³-C(S)N(R³)₂, -NR³-C[=N(R³)]-N(R³)₂, -N(R³)-C[=N-NO₂]-N(R³)₂, -N(R³)-C[=N-NO₂]-OR³, -OC(O)R³, -OC(S)R³, -OC(O)N(R³)₂, -C(O)N(R³)-N(R³)₂, -N(R³)-N(R³)C(O)R³, -N(R³)-OC(O)R³, -N(R³)-OC(O)R³, -N(R³)-OC(O)R³, -OC(S)N(R³)₂, -OC(S)N(R³)(R³), or -PO₃-R³;

E is selected from Ht; [O-Ht;] Ht-Ht; Ht fused with Ht; -O-R³; -N(R²)(R³); [-N(R²)-Ht;] C₁-C₆ alkyl, which is optionally substituted with one or more groups selected from R⁴ or Ht; C₂-C₆ alkenyl, which is optionally substituted with one or more groups selected from R⁴ or Ht; C₃-C₆ saturated carbocycle, which is optionally substituted with one or more groups selected from R⁴ or Ht; or C₅-C₆ unsaturated carbocycle, which is optionally substituted with one or more groups selected from R⁴ or Ht;

each R⁴ is independently selected from -R², -OR², -OR³, -SR², -SOR², -SO₂R², -CO₂R², -OC(O)-R², -C(O)-N(R²)₂, -C(O)-NR²(OR²), -S(O)₂-N(R²)₂, halo, -NR²-C(O)-R², -NR²-OR², -N(R²)₂ or -CN;

each R⁷ is independently selected from hydrogen,



wherein each M is independently selected from H, Li, Na, K, Mg, Ca, Ba, $-\text{N(R}^2\text{)}_4$, $\text{C}_1\text{--C}_{12}\text{--alkyl}$, $\text{C}_2\text{--C}_{12}\text{--alkenyl}$, or $-\text{R}^6$; wherein 1 to 4 $-\text{CH}_2$ radicals of the alkyl or alkenyl group, other than the $-\text{CH}_2$ that is bound to Z, is optionally replaced by a heteroatom group selected from O, S, S(O) , S(O)_2 , or $\text{N(R}^2\text{)}$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, $-\text{C}_1\text{--C}_4$ alkyl, $-\text{N(R}^2\text{)}_2$, $-\text{N(R}^2\text{)}_3$, $-\text{OH}$, $-\text{O--(C}_1\text{--C}_4\text{ alkyl)}$, $-\text{CN}$, $-\text{C(O)OR}^2$, $-\text{C(O)--N(R}^2\text{)}_2$, $\text{S(O)}_2\text{--N(R}^2\text{)}_2$, $-\text{N(R}^2\text{)--C(O)--R}_2$, C(O)R^2 , $-\text{S(O)}_n\text{--R}^2$, $-\text{OCF}_3$, $-\text{S(O)}_n\text{--R}^6$, $-\text{N(R}^2\text{)--S(O)}_2\text{(R}^2\text{)}$, halo, $-\text{CF}_3$, or $-\text{NO}_2$;

M' is H, $\text{C}_1\text{--C}_{12}\text{--alkyl}$, $\text{C}_2\text{--C}_{12}\text{--alkenyl}$, or $-\text{R}^6$; wherein 1 to 4 $-\text{CH}_2$ radicals of the alkyl or alkenyl group is optionally replaced by a heteroatom group selected from O, S, S(O) , S(O)_2 , or $\text{N(R}^2\text{)}$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, $-\text{OR}^2$, $-\text{C}_1\text{--C}_4$ alkyl, $-\text{N(R}^2\text{)}_2$, $\text{N(R}^2\text{)}_3$, $-\text{OH}$, $-\text{O--(C}_1\text{--C}_4\text{ alkyl)}$, $-\text{CN}$, $-\text{C(O)OR}^2$, $-\text{C(O)--N(R}^2\text{)}_2$, $-\text{S(O)}_2\text{--N(R}^2\text{)}_2$, $-\text{N(R}^2\text{)--C(O)--R}_2$, $-\text{C(O)R}^2$, $-\text{S(O)}_n\text{--R}^2$, $-\text{OCF}_3$, $-\text{S(O)}_n\text{--R}^6$, $-\text{N(R}^2\text{)--S(O)}_2\text{(R}^2\text{)}$, halo, $-\text{CF}_3$, or $-\text{NO}_2$;

x , when associated with R^7 , is 0 or 1;

Z is O, S, $\text{N(R}^2\text{)}_2$, or, when M is not present,

H[.] ;

Y is P or S;

X is O or S; [and]

R^9 is $\text{C(R}^2\text{)}_2$, O or $\text{N(R}^2\text{)}$; [and] wherein when Y is S, Z is not S; and

R^6 is a 5-6 membered saturated, partially saturated or unsaturated carbocyclic or heterocyclic ring system, or an 8-10 membered saturated, partially saturated or unsaturated bicyclic ring system; wherein any of said

heterocyclic ring systems contains one or more heteroatoms selected from O, N, S, S(O)_n or N(R²); and wherein any of said ring systems optionally contains 1 to 4 substituents independently selected from -OH, -C₁-C₄ alkyl, -O-(C₁-C₄ alkyl) or -O-C(O)-(C₁-C₄ alkyl).

2. (Amended) The compound according to claim 1, wherein R⁸ is -C₁-C₄-branched or straight chain alkyl, wherein one to two carbon atoms in said alkyl are independently replaced by W, wherein R⁸ is additionally and optionally substituted with one or more groups independently selected from -OH; -C₁-C₄-alkoxy; [-Ht; -O-Ht;] -Ht'; -O-Ht'; -NR²-CO-N(R²)₂; -CO-N(R²)₂; -R¹-C₂-C₆ alkenyl, which is optionally substituted with one or more groups independently selected from hydroxy, C₁-C₄ alkoxy, [Ht, -O-Ht,] -Ht', -O-Ht', -NR²-CO-N(R²)₂ or -CO-N(R²)₂; or R⁷; and

wherein W is -O-, -NR²-, -NR²-S(O)₂-, -NR²-C(O)O-, -O-C(O)NR²-, -NR²-C(O)NR²-, -NR²-C(S)NR²-, -NR²C(O)-, -C(=NR²)-, -C(O)NR²-, -NR²-C(=N-CN)-NR²-, -NR²C(=N-CN)O- or -C(O)O-; and

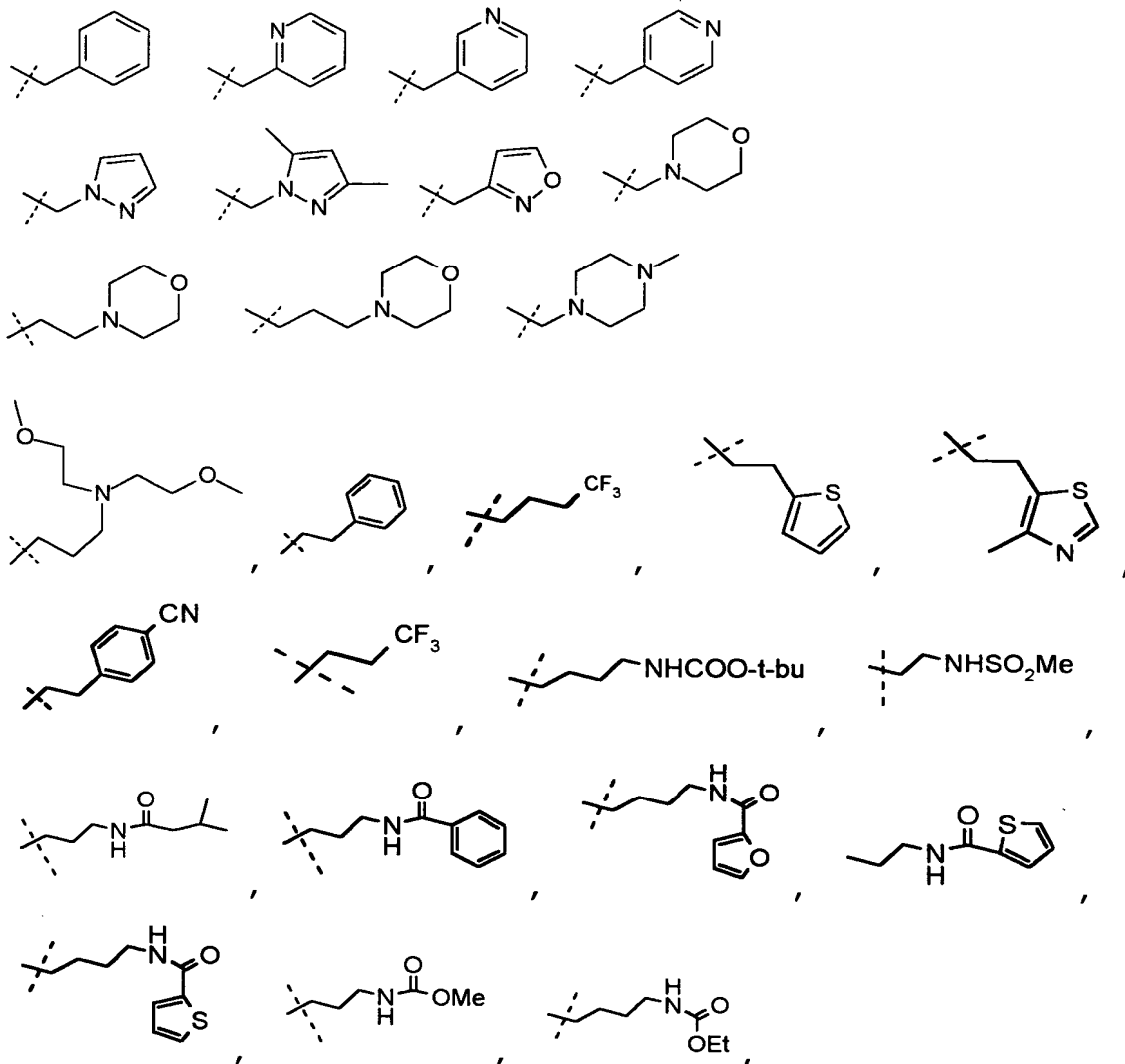
wherein Ht, R¹, R² and R⁷ are as defined in claim 1].

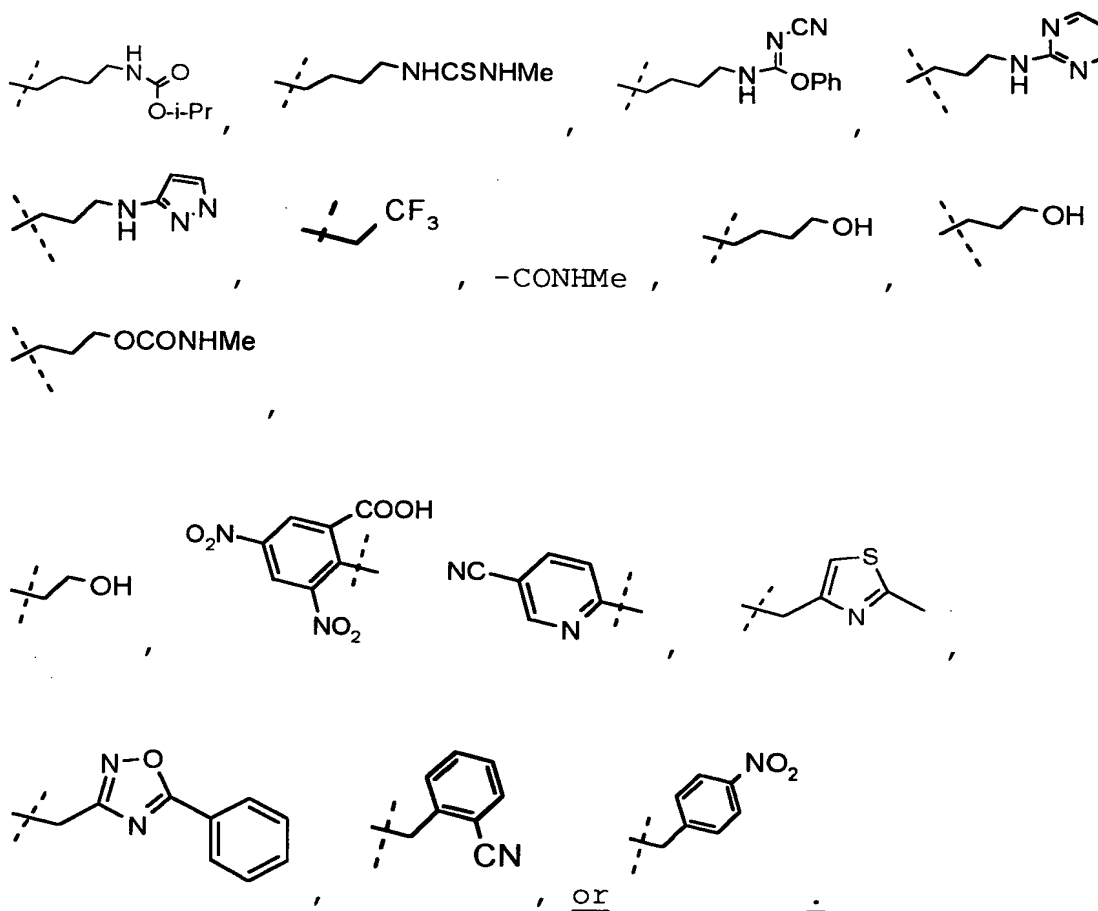
3. (Amended) The compound according to claim 1, wherein R⁸ is a -C₁-C₄-branched or straight alkyl chain, wherein one to two carbon atoms are substituted with [Ht] Ht';

wherein [Ht] Ht' is C₆₋₁₄ aryl or a 5-7 membered saturated or unsaturated heterocycle, containing one or more heteroatoms selected from N, N(R²), O, S and S(O)_n, wherein any member of [Ht] Ht' is optionally substituted with one or more substituents independently selected from oxo, -OR², SR², -R², -N(R²)(R²), -R²-OH, -CN, -CO₂R², -C(O)-N(R²)₂, -S(O)₂-N(R²)₂, -N(R²)-C(O)-R², -N(R²)-C(O)O-R², -C(O)-R², -S(O)_n-R², -OCF₃, [-S(O)_n-Q] -S(O)_n-Q', methylenedioxy,

$-N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$, $-NO_2$, $[Q, -OQ]$ Q' , $-OQ'$, $-OR^7$, $-SR^7$, $-R^7$, $-N(R^2)(R^7)$ or $-N(R^7)_2$ [;] .

4. (Amended) The compound according to claim 1, wherein R^8 is selected from:

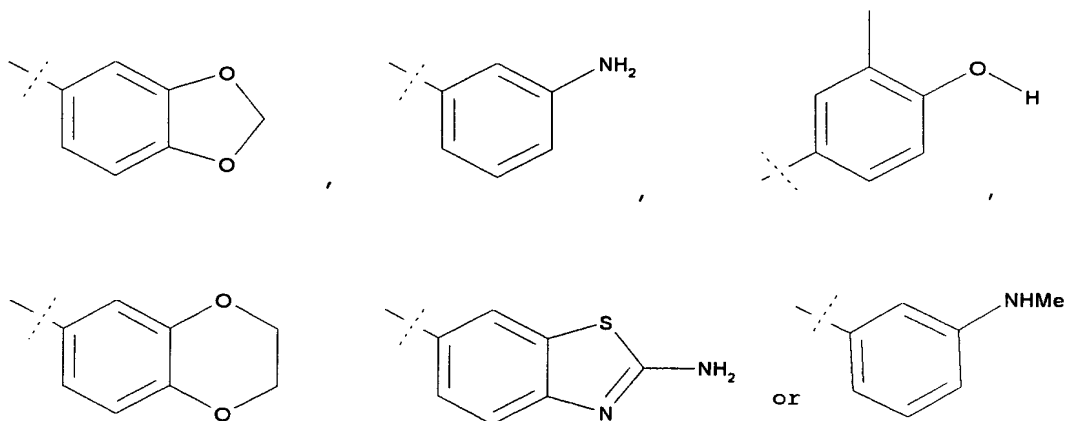




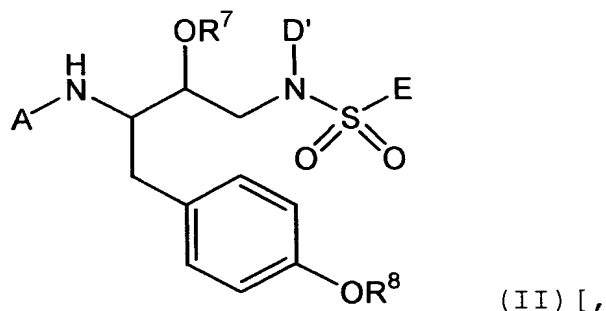
Claim 6 has been canceled.

8. (Amended) The compound according to claim 1, wherein:

E is selected from:

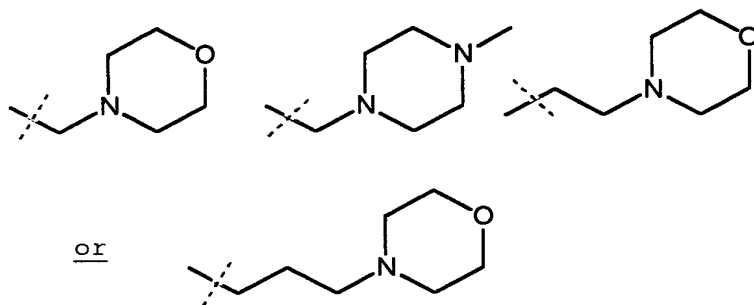


9. (Amended) The compound according to claim 1, having the formula (II):

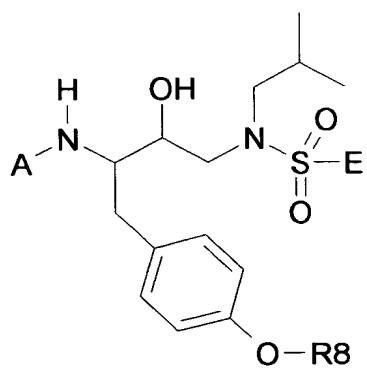


wherein A, R⁷, D', R⁸ and E are as defined in claim 1].

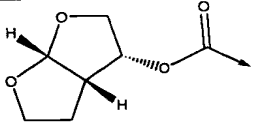
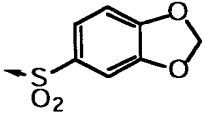
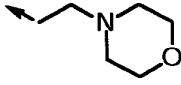
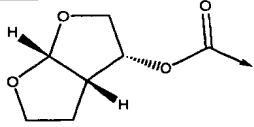
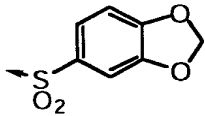
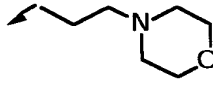
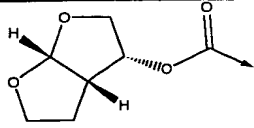
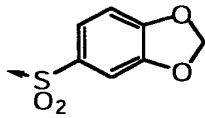
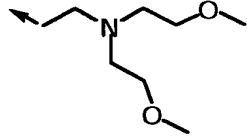
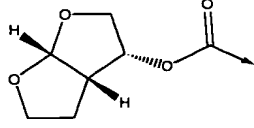
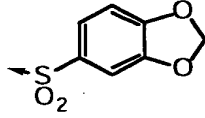
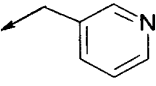
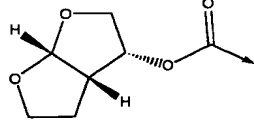
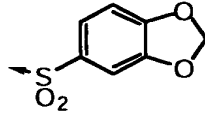
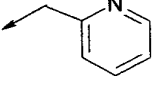
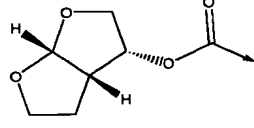
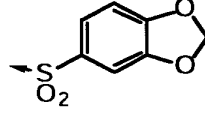
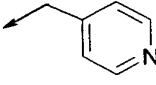
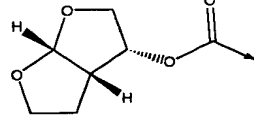
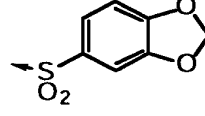
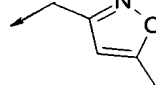
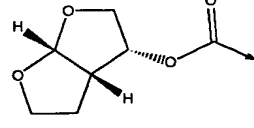
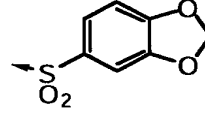
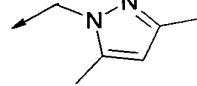
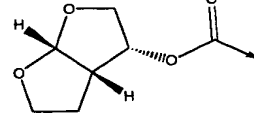
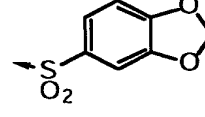
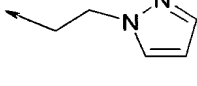
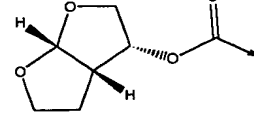
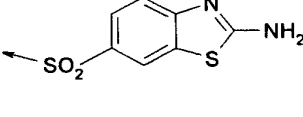
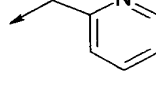
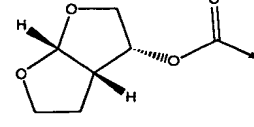
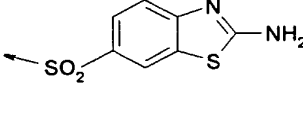
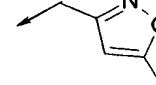
11. (Amended) The compound according to claim 9, wherein R⁸ is selected from:

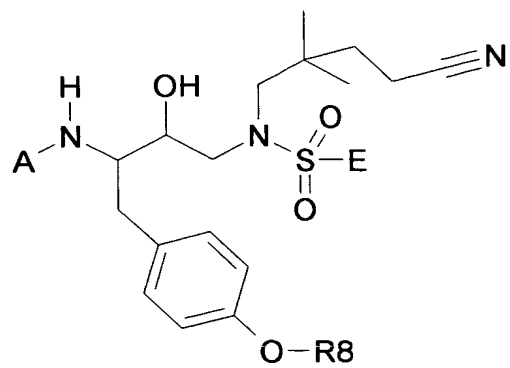


15. (Amended) The compound according to claim 9, wherein said compound is selected from compound numbers: [18, 19, 20, 22, 24, 25,] 26, 27, 31, 33, 35, 36, 38, 41, 43, 48, 49, 51, 52, 53, 54, 55, 56, 57, [58,] 59, 60, [68, 69,] 71, 72, 73, 74, 202-204, 209, 213, 215, 217, 223, 227, 231, 233, 236, 237, 239, 243, 247, 250, 260, 263, 271, 281, 289, 293, 295, 304, 309, 317, 319, 320, 322, 334, 335, 348, 364, 367, 368, 375, 382, 383 [and] or 396[.] , wherein said compound is as defined below:

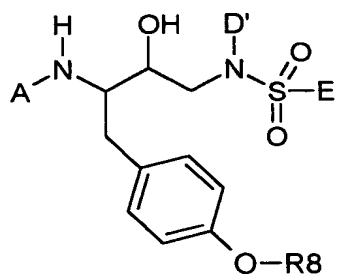


2	S(O) ₂ E	R ⁸
26		
27		
31		
33		
35		
36		
38		
41		
43		

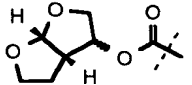
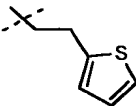

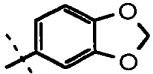
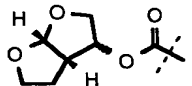
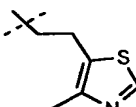

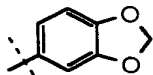
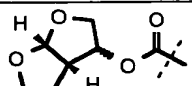
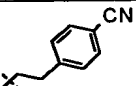

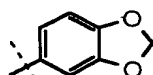
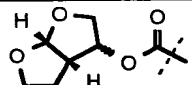
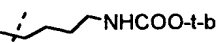

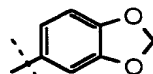
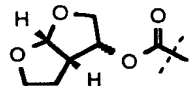


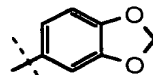
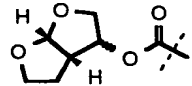
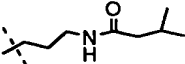

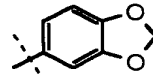
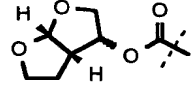
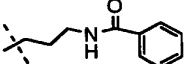

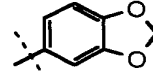
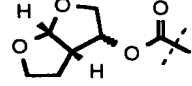
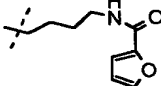

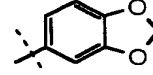
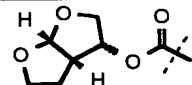
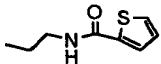

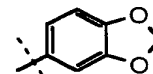
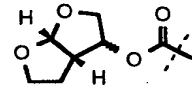
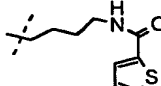

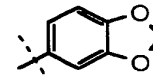
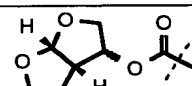
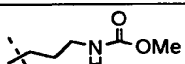

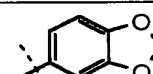
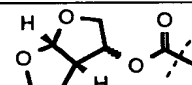
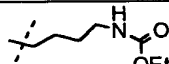

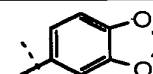
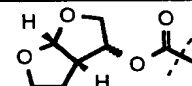
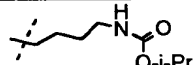

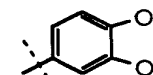
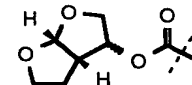


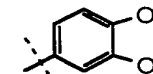
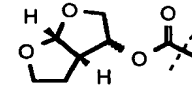
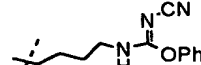

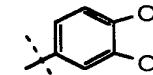
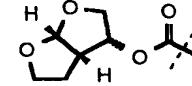
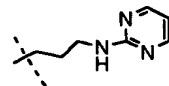

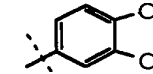
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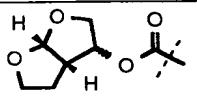
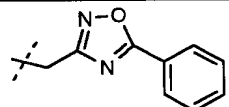
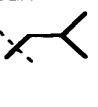
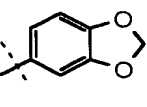
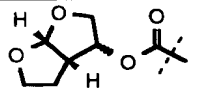
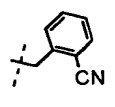
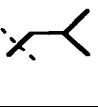
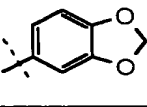
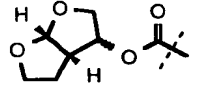
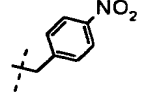
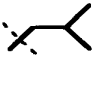
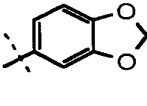
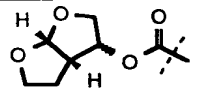
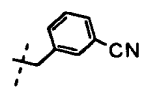
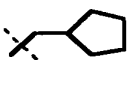
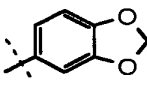


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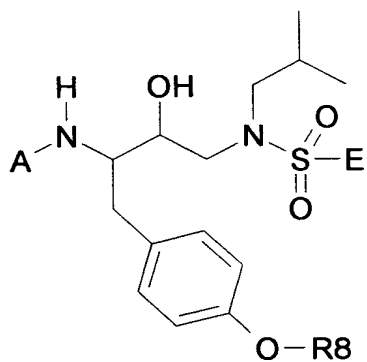
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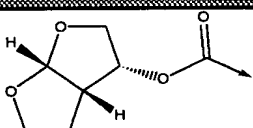
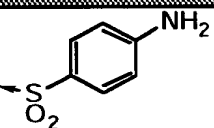
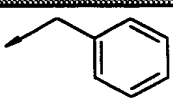
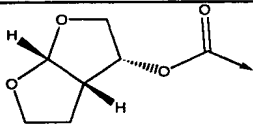
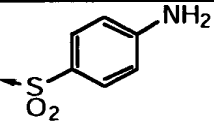
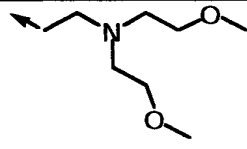
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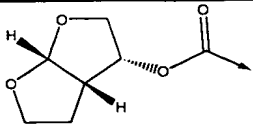
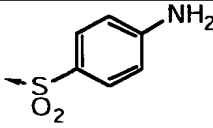
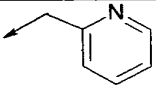
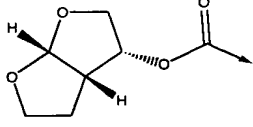
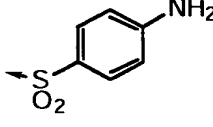
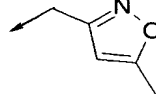
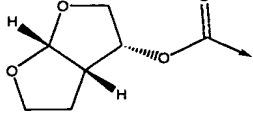
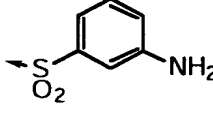
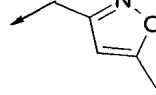
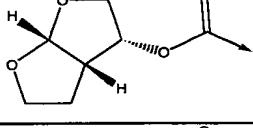
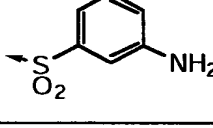
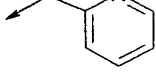
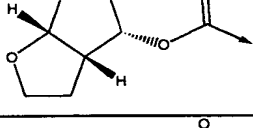
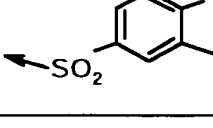
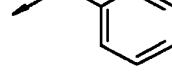
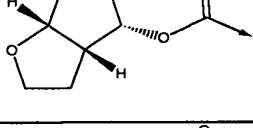
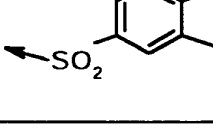
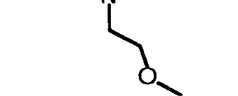
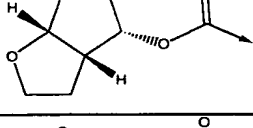
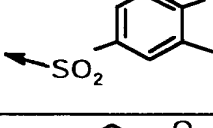
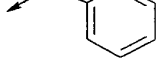
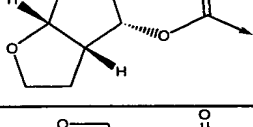
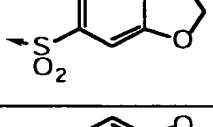
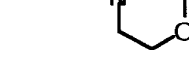
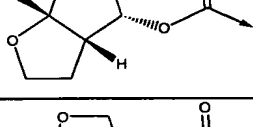
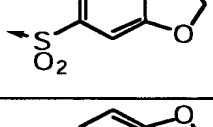

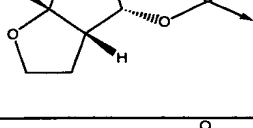
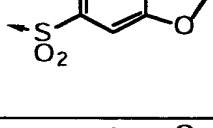
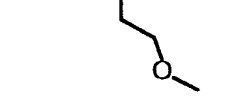
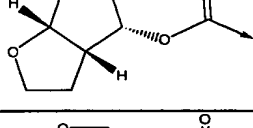
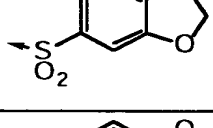
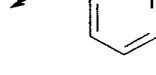
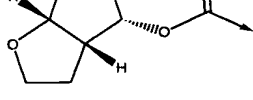
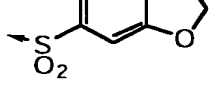
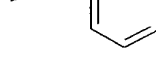
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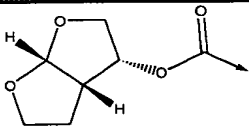
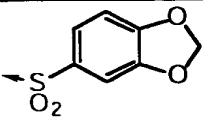
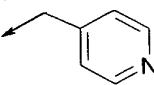
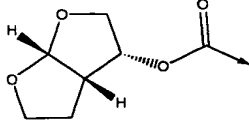
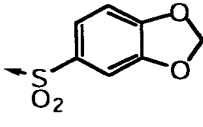
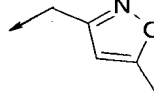
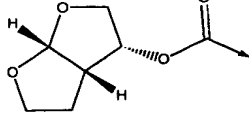
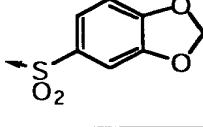
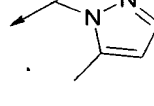
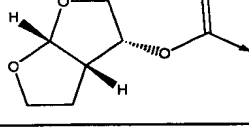
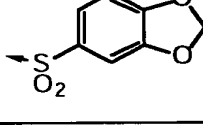
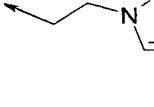
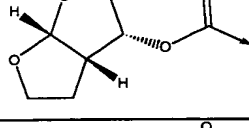
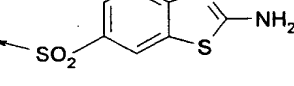
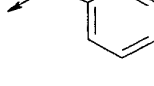
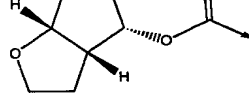
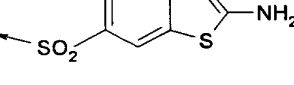

375				
382				
383				
396				

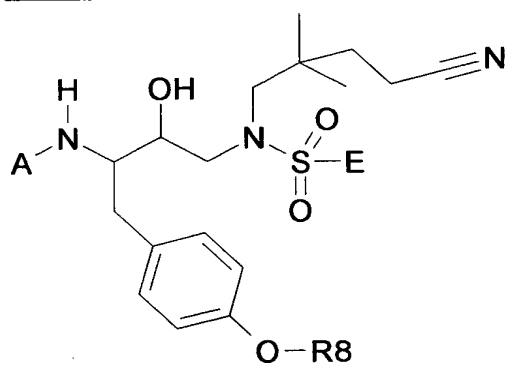
16. (Amended) The compound according to claim 15, wherein said compound is selected from compound numbers: 26, 27, 31, 33, 35, 36, 38, 41, 43, 48, 49, 51, 52, 53, 54, 55, 56, 57, [58,] 59, 60, [69,] 71, 72, 73, 74, 209, 215, 227, 233, 237, 281, 289, 295, 304, 309, 322, 335, 364, 368, 382 [and] or 383[.], wherein said compound is as defined below:

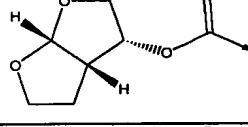
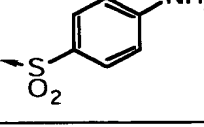
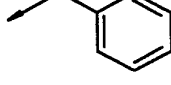
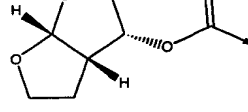
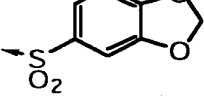
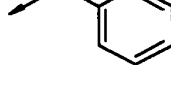


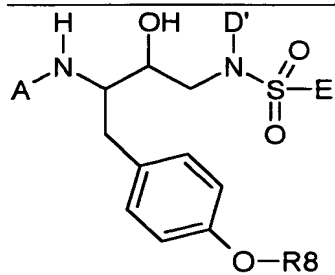
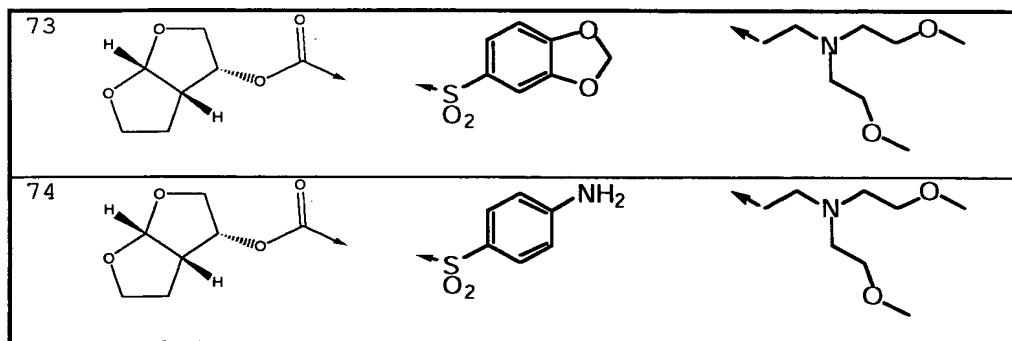
A	S(O) ₂ E	R
26 		
27 		

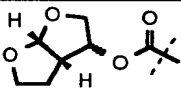
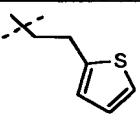

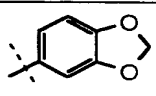
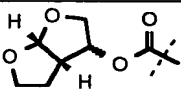
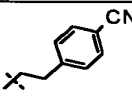

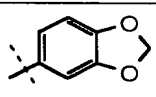
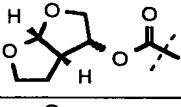


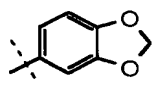
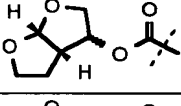
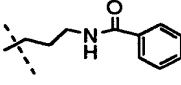

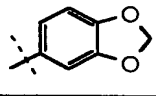
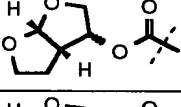
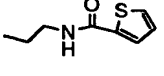

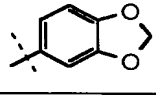
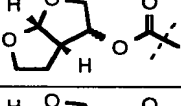
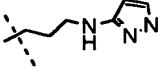

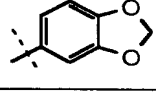
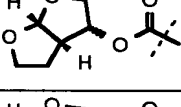
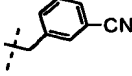

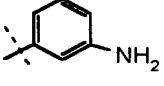
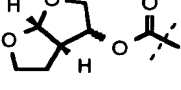


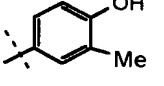
Z	S(O) ₂ E	P
31 		
33 		
35 		
36 		
38 		
41 		
43 		
48 		
49 		
51 		
52 		
53 		

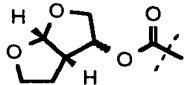

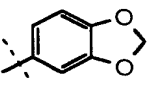
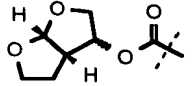


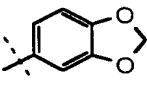
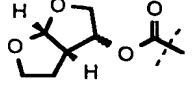
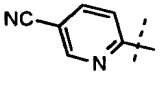

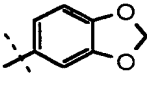
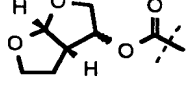


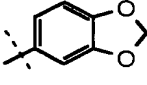
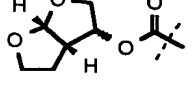
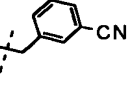

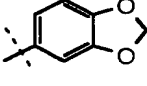
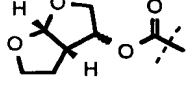
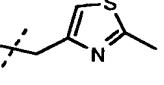

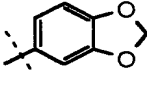
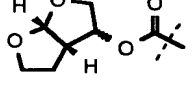


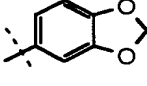
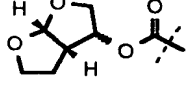
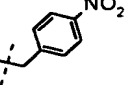

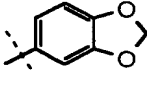
A	S(O) ₂ E	P
54 		
55 		
56 		
57 		
59 		
60 		



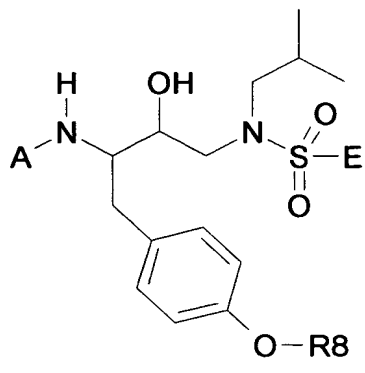
A	S(O) ₂ E	P
71 		
72 		

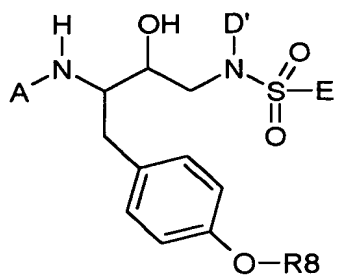
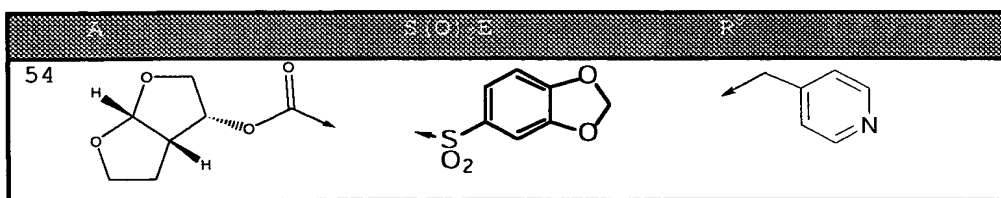


	A	R ^B	D'	E
209				
215				
227				
233				
237				
281				
289				
295				

	A	R ^B	D'	E
309		-CONHMe		
322				
335				
364				
367				
368				
382				
383				

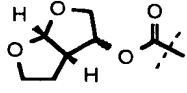
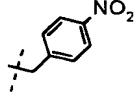

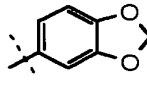
17. (Amended) The compound according to claim 16, wherein said compound is selected from: 54, 209, 237, 281, 295, 309, 367 [and] or 368[.], wherein said compound is as defined below:





	A	R ^B	D'	E
209				
237				
281				
295				

	A	R ^B	D'	E
309		-CONHMe		
367				
368				
382				

383				
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18. (Amended) A composition comprising a compound according to any one of claims [1 to 17] 1-5 or 7-17, in an amount sufficient to inhibit an aspartyl protease; and a pharmaceutically acceptable carrier.

21. (Amended) The composition according to claim 18, wherein said composition comprises at least one additional therapeutic agent selected from (1 alpha, 2 beta, 3 alpha)-9-[2,3-bis(hydroxymethyl)cyclobutyl]- guanine [(-)BHCG, SQ-34514]; oxetanocin-G (3,4-bis-(hydroxymethyl)-2-oxetanosyl]guanine); acyclic nucleosides[, such as acyclovir, valaciclovir, famciclovir, ganciclovir or penciclovir]; acyclic nucleoside phosphonates[, such as (S)-1-(3-hydroxy-2-phosphonyl-methoxypropyl)cytosine (HPMPC)]; ribonucleotide reductase inhibitors[, such as 2-acetylpyridine 5-[(2-chloroanilino)thiocarbonyl]thiocarbonohydrazone, 3'-azido-3'-deoxythymidine]; other 2',3'-dideoxynucleosides [such as 2',3'-dideoxycytidine, 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine, or 2',3'-didehydrothymidine]; other aspartyl protease inhibitors[, such as indinavir, ritonavir, nelfinavir, or [3S-[3R*(1R*, 2S*)]]-[3[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-tetrahydro-3-furanyl ester (amprenavir)]; oxathiolane nucleoside analogues[, such as (-)-cis-1-(2-hydroxymethyl)-1,3-oxathiolane 5-yl)-cytosine (lamivudine) or cis-1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-5-fluorocytosine (FTC)]; 3'-deoxy-3'-fluorothymidine; 5-chloro-2',3'-dideoxy-3'-fluorouridine; (-)-cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol; ribavirin; 9-[4-hydroxy-2-(hydroxymethyl)but-1-yl]-guanine (H2G); tat inhibitors[, such as 7-chloro-5-(2-pyrryl)-3H-

1,4-benzodiazepin-2-(H)one (Ro5-3335) or 7-chloro-1,3-dihydro-5-(1H-pyrrol-2yl)-3H-1,4-benzodiazepin-2-amine (Ro24-7429)]; interferons[, such as α -interferon]; renal excretion inhibitors [such as probenecid]; nucleoside transport inhibitors [such as dipyridamole]; pentoxifylline; N-acetylcysteine (NAC); Procyteine; α -trichosanthin; phosphonoformic acid; immunomodulators[, such as interleukin II or thymosin]; granulocyte macrophage colony stimulating factors; erythropoetin; soluble CD₄ and genetically engineered derivatives thereof; non-nucleoside reverse transcriptase inhibitors (NNRTIs)[, such as nevirapine (BI-RG-587), zalcitabine (α -AZA) or delaviridine (BHAP)]; [phosphonoformic acid;] 1,4-dihydro-2H-3,1-benzoxazin-2-ones NNRTIs[, such as (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one (L-743,726 or DMP-266)]; or quinoxaline NNRTIs[, such as isopropyl (2S)-7-fluoro-3,4-dihydro-2-ethyl-3-oxo-1(2H)-quinoxalinecarboxylate (HBY1293)].

22. (Amended) The composition according to any one of claims 18-21 or 28, wherein said composition is in an orally available dosage form.

Claim 28 has been added.

28. (Added) The composition according to claim 21, wherein said acyclic nucleosides are acyclovir, valaciclovir, famciclovir, ganciclovir or penciclovir; said acyclic nucleoside phosphonates are (S)-1-(3-hydroxy-2-phosphonyl-methoxypropyl)cytosine (HPMPC); said ribonucleotide reductase inhibitors are 2-acetylpyridine 5-[(2-chloroanilino)thiocarbonyl] thiocarbonohydrazone, or 3'-azido-3'-deoxythymidine; said other 2',3'-dideoxynucleosides are 2',3'-dideoxycytidine, 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine, or 2',3'-didehydrothymidine; said other aspartyl protease inhibitors

are indinavir, ritonavir, nelfinavir, or [3S-[3R*(1R*, 2S*)]]-[3[[(4-aminophenyl)sulfonyl] (2-methylpropyl) amino]-2-hydroxy-1-(phenylmethyl)propyl]-tetrahydro-3-furanyl ester (amprenavir); said oxathiolane nucleoside analogues are (-)-cis-1-(2-hydroxymethyl)-1,3-oxathiolane 5-yl)-cytosine (lamivudine) or cis-1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-5-fluorocytosine (FTC); said tat inhibitors are 7-chloro-5-(2-pyrrolyl)-3H-1,4-benzodiazepin-2-(H)one (Ro5-3335) or 7-chloro-1,3-dihydro-5-(1H-pyrrol-2yl)-3H-1,4-benzodiazepin-2-amine (Ro24-7429); said interferons are α -interferon; said renal excretion inhibitors are probenecid; said nucleoside transport inhibitors are dipyridamole; said immunomodulators are interleukin II or thymosin; said non-nucleoside reverse transcriptase inhibitors (NNRTIs) are nevirapine (BI-RG-587), zalcitabine (α -APA) or delaviridine (BHAP); said 1,4-dihydro-2H-3,1-benzoxazin-2-ones NNRTIs are (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one (L-743,726 or DMP-266); or said quinoxaline NNRTIs are isopropyl (2S)-7-fluoro-3,4-dihydro-2-ethyl-3-oxo-1(2H)-quinoxalinecarboxylate (HBY1293).